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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/085,239	WARD ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42 and 44-46* is/are rejected.

7)☒ Claim(s) *40,43,47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 40-47 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed May 7, 2010 was received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 40-47 remain pending. Claims 40-42 and 44-46 are amended. Claims 48-51 are cancelled.

Applicant's arguments, filed May 7, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Objection to the Claims

Claims 43 and 47 remain objected to for depending upon a rejected base claim, but would otherwise be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Objection to the Claims (New Grounds of Objection)

Claim 40 is objected to for reciting the term "actinic ketatosis", which is properly ---actinic keratosis---. Correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 40 is directed to a method of treating a hyperproliferative disease of the skin selected from the group consisting of psoriasis, acne vulgaris, actinic keratosis, solar keratosis, squamous carcinoma in situ, cancers and premalignant conditions, ichthyoses, hyperkeratosis and disorders of keratinization, consisting of administering to a patient in need of treatment for a hyperproliferative disease of the skin a pharmaceutical composition consisting of carbenoxolone and one or more pharmaceutically acceptable excipients.

In particular, the instant claim is directed to a method of treating a hyperproliferative disease of the skin, but further defines the diseases to be treated as including, *inter alia*, cancers and premalignant conditions, which is a broader genus of diseases than that specifically recited in the preamble (i.e., specifically, diseases of the skin). It is unclear whether Applicant intends for the "cancers and premalignant conditions" recited in the instant claims to be limited only to those that occur in the skin or if Applicant intends for the claim to cover, generically, any type of cancer or premalignant condition *per se*. The claim as presently written fails to clearly, precisely or deliberately set forth the scope of the cancers and/or premalignant conditions intended to be circumscribed by the instant claims. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection.

For these reasons, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is, thus, properly rejected.

Claim Rejections - 35 USC § 102 (New Grounds of Rejection)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Gottfried et al. (GB 2023001 A; 1979).

Gottfried et al. teaches pharmaceutical compositions for treating, alleviating and ameliorating the symptoms of cancer in humans that comprise at least one glycyrrhetinic acid derivative compound or a pharmaceutically compatible salt thereof in admixture with a pharmaceutical diluent or carrier (abstract), wherein the compound is, *inter alia*, glycyrrhetinic acid hemisuccinate (also known as carbenoxolone sodium; p.2, l.7-11). Gottfried et al. discloses that the compositions may be administered orally, rectally, vaginally or by injection for the treatment of neoplasms and various forms of cancer, such as, e.g., neoplastic diseases of the gastrointestinal tract, vagina, uterus or mammary glands (abstract; p.1, l.62-65). Gottfried et al. further teaches that the diluent or carrier may be, *inter alia*, water as an injection medium, tartrate, citrate and borate buffers; ethanol; dimethylsulphoxide, starch, lactose, mannitol, etc. (i.e., an "excipient" as instantly claimed; p.1, l.46-61).

Note that the instant claims do not specifically and clearly set forth the types of cancers and/or premalignant conditions to be treated (i.e., whether they are particularly limited to those of the skin or not) and, therefore, the claim is understood to read on various different types of cancers that are not so limited to the skin, absent factual evidence to the contrary (see *supra* the rejection under 35 U.S.C. 112, second paragraph). In view of the fact that Gottfried et al. clearly teaches the claimed compound (i.e., carbenoxolone sodium) for the treatment of neoplastic diseases and cancers comprising administering a composition of the claimed compound in combination with an excipient, the rejection is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-42 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burchardt et al. (WO 97/15298; 1997), already of record, for the reasons of record set forth at p.4-10 of the previous Office Action dated July 7, 2009, of which said reasons are herein incorporated by reference.

Newly amended claims 40-42 and 44-46 remain properly included in the present rejection because Burchardt et al. teaches the treatment of acute and chronic inflammatory disorders, such as psoriasis (p.6, l.1-11), using a glucocorticoid, of which carbenoxolone sodium is specifically named, and an LTD_4 receptor antagonist (p.1, l.4-6 and p.2, l.3-7). Burchardt et al. expressly discloses that the combination can be used topically as an ointment or cream for application to the skin (p.6, l.18-20).

Applicant states at p.71, l.11-18, of the instant specification that, "Suitable pharmaceutically acceptable carriers are well known in the art and vary with the desired form and mode of administration of the pharmaceutical formulation. For example, they can include diluents or excipients such as fillers, binders, wetting agents, disintegrators, surface-active agents, lubricants and the like. Typically, the carrier

is a solid, a liquid or a vaporizable carrier, or a combination thereof. Each carrier should be 'acceptable' in the sense of being compatible with the other ingredients in the formulation and not injurious to the patient. The carrier should be biologically acceptable without eliciting an adverse reaction (e.g., immune response) when administered to the host." Though Applicant refers to a "carrier" in this portion of the disclosure, it is understood to apply equally to the terms "diluents" or "excipients" since the instant specification clearly states that the pharmaceutically acceptable carriers suitable for use in the present invention include diluents or excipients. Accordingly, the same properties to which Applicant refers as being applicable to "carriers" are understood to be applicable to the diluents or excipients usable in the invention as well, in view of this disclosure and absent factual evidence to the contrary.

In light of these properties of the claimed "excipients" for use in the present invention, the LTD_4 receptor antagonist of Burchardt et al. meets Applicant's limitation directed to a "pharmaceutically acceptable excipient" because (1) it is clearly compatible with the other agents in the formulation, (2) is also clearly not injurious to the subject to be treated, since it is formulated specifically for pharmaceutical use, and (3) does not produce an adverse reaction, such as an adverse immune reaction, since it is taught by Burchardt et al. to treat acute and chronic inflammatory processes via LTD_4 antagonism, which produces a desirable antagonizing effect on leukotriene production in order to treat inflammation (i.e., does not produce an *adverse immune reaction*). Accordingly, Burchardt et al. provides for the (topical) administration of a composition consisting of carbenoxolone with an LTD_4 receptor antagonist (i.e., in this case, equivalent to the "excipient" of the instant claims) to a subject (or the affected skin of said subject) in need of treatment of psoriasis, which meets Applicant's limitations of claims 40-42 and 44-46.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Remington's teaches that excipients are needed to stabilize the active pharmaceutical ingredient by providing antioxidant, heavy-metal chelating

or light protection properties, or may also be used to enhance bioavailability and to control the release from dosage forms. Applicant cites two internet sources to define the term excipient as "pharmaceutical additives, the inactive ingredients used to make up a medication...include dyes, flavors, binders, emollients, fillers, lubricants, preservatives, and many more classifications…cornstarch, lactose, talc, magnesium stearate, sucrose, gelatin, calcium stearate, silicon dioxide, shellac and glaze" or "an inert substance, which is added to a drug to provide bulk, e.g., in tablets" (see Exhibits B-C). Applicant further references a publication of Pifferi et al. (Exhibit D) to define an excipient as an inert substance added to a prescription to confer a suitable consistency and concludes that the LTD_4 receptor antagonist as used in Burchardt et al. could not be considered a pharmaceutically acceptable excipient in view of these definitions.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant cites to Remington's to teach that excipients are needed to stabilize the active pharmaceutical ingredient by providing antioxidant, heavy-metal chelating or light protection properties, or may also be used to enhance bioavailability and to control the release from dosage forms. This is unpersuasive because these statements have not been considered in their full context. Specifically, Remington's teaches that, "Excipients serve many roles and are the backbone of a formulation" (col., para.2, p.741) and then goes on to state that they "*may be* needed" (emphasis added) for stabilization of the active pharmaceutical ingredient (API) by providing antioxidant, heavy-metal chelating, or light–protection properties, or enhance bioavailability and to control the release from dosage forms. The use of the phrase "may be needed" as used in Remington's is clearly indicative of the fact that these are exemplary functions of an excipient and do not so limit the term "excipients" to only those that have the recited functions relied upon by Applicant. In fact, when considered in context, Remington's clearly states that "excipients" serve various roles in a formulation, of which those that are subsequently discussed are merely exemplary. As a result, Applicant's urging that the LTD_4 receptor antagonist of Burchardt et al.

could not be considered a “pharmaceutically acceptable excipient” as defined by Remington’s because it does not have the properties recited therein is clearly unpersuasive because these properties are merely exemplary and do not serve to limit the scope of excipients to only those that function in the manner disclosed in the reference.

Secondly, Applicant cites an internet source as Exhibit B to further define the term excipient. This is also unpersuasive. Exhibit B defines an excipient as "pharmaceutical additives, the inactive ingredients used to make up a medication" and provides an exemplary list of additives (i.e., as evidenced by the term "include", which clearly indicates that the list is exemplary and non-limiting) that include, *inter alia*, dyes, flavors, binders, emollients, fillers, lubricants, preservatives, starch lactose, etc. The description of an "excipient" as an "additive" and an "inactive ingredient in a medication" fails to provide any substantial clarification of what would be included or excluded from the term "excipient". This is because the term “inactive” is a relative term to define the level of “activity” of the excipient and, thus, the description of an excipient as an “inactive” ingredient appears to be a description of the activity of the ingredient as compared to, e.g., the API in the medicament. Thus, it is not that the excipient itself completely lacks activity, but rather that the excipient has less activity as compared to the API contained in the medicament. For example, water is frequently used as a pharmaceutical excipient and is also essential for various metabolic processes and is required for adequate hydration. Such effects clearly constitute “biological activity”, which contradicts the idea that the excipient is devoid of "activity". However, its pharmacologic activity would not be as substantial as the API contained in a formulation of the two components. Accordingly, it is clear that the cited definition of Exhibit B defines the "inactivity" relative to the active pharmaceutical ingredient. Because the carbenoxolone compound and the LTD_4 receptor antagonist each function with a distinct mechanism of action (i.e., a glucocorticosteroid versus a LTD_4 receptor antagonist), the LTD_4 receptor antagonist would also be considered "inactive" relative to a

glucocorticosteroid because it lacks any functionality as a glucocorticosteroid, absent factual evidence to the contrary, and, therefore, also clearly be an excipient as claimed.

Exhibit B further defines three properties of a pharmaceutical additive (i.e., excipient): (1) be safe in the amount used in the drug; (2) not affect the bioavailability and performance of the drug; and (3) be manufactured in accordance with good standards. Each of these three requirements is met by the LTD_4 receptor antagonist of Burchardt et al. because: (1) the antagonist is formulated specifically for pharmaceutical use and is, thus, safe for administration; (2) the antagonist is clearly compatible with the other agents in the formulation and, thus, does not affect the bioavailability and performance of the glucocorticosteroid; and (3) is understood to be manufactured in accordance with good standards as a result of its pharmaceutical acceptability. Thus, it is clear that Applicant's reliance on Exhibit B does not exclude consideration of the LTD_4 receptor antagonist of Burchardt et al. as a pharmaceutically acceptable excipient.

Thirdly, Applicant relies upon Exhibit C and the publication to Pifferi et al. to define the term excipient as, respectively, "an inert substance, which is added to a drug to provide bulk, e.g., in tablets" (Exhibit C) or "an inert substance added to a prescription to confer a suitable consistency" (Pifferi et al.). These arguments are unpersuasive. Though it is noted that Exhibit C defines an excipient as "an inert substance, which is added to a drug to provide bulk, e.g., in tablets", this definition is seemingly contradicted by Pifferi et al. Specifically, Pifferi et al. teaches, "Medicinal products can be considered a dosed combination of two types of constituents: the active principles and the excipients. The latter are the more important as far as weight is concerned, whether in solid forms, suspensions or solutions. The ideal excipient should be able to fill numerous and important functions, first among which that of guaranteeing the dose, stability and release of the active principle, and the patient's "compliance". Furthermore, it should possess particular chemical, physical and mechanical characteristics, so as to optimise the formulation's 'performance' both during the manufacturing phase (manufacturability) and when used by

the patient. This multiplicity of roles fit very ill with the traditional galenic view, that saw these 'non-medicinal ingredients' as chemically and pharmaco-toxicologically inert." (col.1-2, p.548)

Pifferi et al. clearly rejects the concept that a pharmaceutical excipient is "chemically and pharmacologically inert", as asserted by the reference of Exhibit C, but rather states that an excipient fulfills very specific roles in a medicinal product, including guaranteeing the dose, stability and release of the active principle, etc. and is not limited to compounds without chemical and/or pharmacologic effect. Such roles are clearly met by the LTD_4 receptor antagonist of Burchardt et al. because the antagonist is clearly pharmaceutically compatible with the carbenoxlone component and, therefore, provides the stability and release of the dose of the glucocorticoid contained therein. Thus, it is clear from the references cited by Applicant that the term "pharmaceutically acceptable excipient" does not explicitly exclude the consideration of the LTD_4 receptor antagonist of Burchardt et al. as an "excipient" as claimed.

Note also that Applicant alleges that Pifferi et al. supports the concept that the excipient should be "inert" by citing the definition provided at col.1, para.1, p.541 of the reference, which states that an excipient is "any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug". However, Pifferi et al. clearly states that this definition is from 1974 and has been changed at least once since that date, as evidenced by Pifferi et al. at col.2, para.2, p.541, which states, "To the function of simple vehicle, galenic science then added that of adjuvant in the carrying and release of the active principle of the formulation. Looking at the matter from this angle, the United States' National Formulary of 1994 states that an excipient is any component other than the active principle added intentionally to the medicinal formulation, or 'everything in the formulation except the active drug'." Clearly, the definition of the term "excipient" has evolved over time, as evidenced by the discussion in Pifferi et al., and, thus, the citation of an outdated definition that has clearly been amended since its issuance to support Applicant's position is clearly unpersuasive in establishing that the LTD_4 receptor antagonist would be excluded from the term "excipient" as recited in the instant claims.

In view of these reasons set forth *supra*, the totality of the evidence of nonobviousness fails to outweigh the evidence of obviousness as set forth *supra* when all of the evidence is considered. Accordingly, in light of the properties of the claimed "excipients" for use in the present invention as disclosed in the instant specification, it is maintained that the LTD_4 receptor antagonist of Burchardt et al. meets Applicant's limitation directed to a "pharmaceutically acceptable excipient" because (1) it is clearly compatible with the other agents in the formulation, (2) is also clearly not injurious to the subject to be treated, since it is formulated specifically for pharmaceutical use, and (3) does not produce an adverse reaction, such as an adverse immune reaction, since it is taught by Burchardt et al. to treat acute and chronic inflammatory processes via LTD_4 antagonism, which produces a desirable antagonizing effect on leukotriene production in order to treat inflammation (i.e., does not produce an *adverse immune reaction*). Accordingly, Burchardt et al. provides for the (topical) administration of a composition consisting of carbenoxolone with an LTD_4 receptor antagonist (i.e., in this case, equivalent to the "excipient" of the instant claims) to a subject (or the affected skin of said subject) in need of treatment of psoriasis, which meets Applicant's limitations of claims 40-42 and 44-46.

For these reasons *supra*, and those previously made of record at p.4-10 of the Office Action dated July 7, 2009, rejection of claims 40-42 and 44-46 is proper.

Conclusion

Rejection of claims 40-42 and 44-46 is proper.

Claims 43 and 47 are objected to for depending from a rejected base claim.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Primary Examiner, Art Unit 1614

July 17, 2010